I. Remarks

Claims 59-116 are pending.

Applicants thank the Examiner for expanding the examination of the application to include additional species encompassed by the compounds of Formula (II) and for the rejoinder of the method and kit claims.

II. First Rejection under 35 U.S.C. §112, First Paragraph

Claims 59-116 are rejected under 35 USC § 112, first paragraph, as lacking enablement.

Applicants respectfully traverse the rejection and respectfully submit that the claims satisfy the requirements under 35 U.S.C. § 112, first paragraph.

The PTO questions whether the compounds of the present invention are pro-drugs. Applicants respectfully submit that one skilled in the art can readily determine that **all** the nitrosated and/or nitrosylated compounds of the present invention are pro-drugs. As indicated in the specification, at for example, page 1, line 31 to page 2, line 3; and page 87, lines 3 to 6 and lines 14 to 16, the COX-2 inhibitors of the present invention have been nitrosated and/or nitrosylated through one or more sites such as oxygen (hydroxyl condensation), sulfur (sulfhydryl condensation) and/or nitrogen atom thereby resulting in an ester, thioester or amide moiety i.e. the compounds will be readily hydrolyzed *in vivo* or *in vitro* to result in the parent COX-2 inhibitor compound (i.e. the non-nitrosylated and/or nitrosated compound) and a linker that contains a –NO and/or -NO_2 group. Additionally, one skilled in the art can readily determine which compounds encompassed by Formula (II) and can also readily determine where the –NO_2 group and/or –NO group is attached to the compound of Formula (II). Only the substituents D_1, V or K will result in a –NO_2 group and/or –NO group in the compound of Formula (II). That which can be so easily and readily determined by one skilled in the art need not be described in detail in the specification.

The PTO also asserts that that there is no support for the claimed utilities of the compounds of the invention alone and as combination therapies. The PTO then further states that the assay presented in the specification of the present invention is limited to showing the selective COX-2 inhibition in whole blood for only one species (Example1). Applicants respectfully submit that Applicants at page 120, Table 1, have shown that **six** compounds, all encompassed by the compound of Formula (II), are COX-2 selective inhibitors.

Additionally there are numerous scientific publications discussing the methods of use of selective COX-2 inhibitor compounds alone or as combination therapies for the treatment of numerous diseases and disorders. In support thereof, Applicants refer to U.S. Patent No. 5,474,995, which was provided to the PTO in the Information Disclosure Statement filed on May 18, 2005. At column 7, lines 31 to column 8, line 20, U.S. Patent No. 5,474,995 states (Emphasis Presented):

> "The Compound of Formula I is useful for the relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, bums, injuries, following surgical and dental procedures. In addition, such a compound may inhibit cellular neoplastic transformations and metastic tumor growth and hence can be used in the treatment of cancer. Compounds of formula I may also be useful for the treatment of dementia including pre-senile and senile dementia, and in particular, dementia associated with Alzheimer Disease (ie Alzheimer's dementia).
>
> Compounds of formula I will also inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labor and asthma.
>
> By virtue of its **high cyclooxygenase-2 (COX-2) activity and/or its selectivity for cyclooxygenase-2 over cyclooxygenase-1 (COX-1)** as defined above, compounds of formula I will prove useful as an alternative to conventional non-steroidal antiinflammatory drugs (NSAID'S) particularly where such non-steroidal antiinflammatory drugs may be contra-indicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; GI bleeding, coagulation disorders including anemia such as hypoprothrombinemia, haemophilia or other bleeding problems (including those relating to reduced or impaired platelet function); kidney disease (e.g. impaired renal function); those prior to surgery or taking anticoagulants; and those susceptable to NSAID induced asthma.

> Similarly, compounds of formula I, will be useful as a partial or complete substitute for conventional NSAID'S in preparations wherein they are presently **co-administered with other agents or ingredients**. Thus in further aspects, the invention encompasses pharmaceutical compositions for treating cyclooxygenase-2 mediated diseases as defined above comprising a non-toxic therapeutically effective amount of the compound of Formula I as defined above and one or more ingredients such as another pain reliever including acetominophen or phenacetin; a potentiator including caffeine; an H2-antagonist, aluminum or magnesium hydroxide, simethicone, a decongestant including phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine; an antiitussive including codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a diuretic; a sedating or non-sedating antihistamine. In addition the invention encompasses a method of treating cyclooxygenase mediated diseases comprising: administration to a patient in need of such treatment a non-toxic therapeutically effect amount of the compound of Formula I, optionally co-administered with one or more of such ingredients as listed immediately above."

In further support that COX-2 inhibitors are useful for the treatment of numerous diseases, Applicants refer to WO 01/81332, a copy of which is submitted in the Information Disclosure Statement filed on May 18, 2005. At page 1, line 22 to page 2, line 15, WO 01/81332 A2 states:

> "Previous NSAIDs have been found to prevent the production of prostaglandins by inhibiting enzymes in the human arachidonic acid/prostaglandin pathway including the enzyme cyclooxygenase (COX). The recent discovery of an inducible enzyme associated with inflammation (named "cyclooxygenase-2 (COX-2)" or "prostaglandin G/H synthase II") provides a viable target of inhibition which more effectively reduces inflammation and produces fewer and less drastic side effects.
>
> Recently, there has been significant research into some of the roles of cyclooxygenase-2. It has been found that the COX-2 is upregulated in benign and malignant tumors (K. Subbaramaiah et al., Proc. Soc. Exp. Biol. Med., 216, 201 (1997)) including lung cancer (T. Hida et al., Anticancer Res., 18, 775-82 (1998)). Barrett's esophagus (K. Wilson, Cancer Res., 58, 2929-34 (1998)) and skin cancer (S. Buchman et al., Carcinogenesis, 19, 723-29 (1998)). It is expresses in airway cells implicated in asthma (P. Barnes et al., Lung Biol. Health Dis., 114, 111-17 (1998)). Cox-2 also has a role in pre-term labor, angiogenesis (M. Tsujii et al. Cell, 93, 705-16 (1998)), vascular rejection

(M. Bustos, J. Clin. Invest., 100, 1150-58 (1997)), HIV induced apoptosis (G. Bagetta et al., Biochem. Biophys. Res. Commun., 244, 819-24 (1998)), neurodegeneration (T. Sandhya et al., Brain Res., 788, 223-31 (1998)), inflammatory bowel disease, colitis (I. Singer et al., Gastroenterology, 115, 297-306 (1998)), cerebral ischemia (S. Nogawa et al., Proc. Natl. Acad. Sci., 95, 10966-71 (1998)), and hypertension (A. Nasjletti, Hypertension, 31, 194-200 (1997)), among others.

Drugs that inhibit cyclooxygenase affect colon cancer (T. Kawamori et al., Cancer Res., 58, 409-12 (1998)), allergic neuritis (K. Miyamoto et al., Neuro Report, 9, 2331-4 (1998)), dementia, burn infections (M. Shoup, J. Trauma: Inj., Infec., Crit care, 45, 215-21 (1998)), cytomegalovirus infectivity (E. Speir et al., Circ. Res., 83, 210-16 (1998)), and limbago (H. Bosch, Curr. Med. Res. Opin., 14, 29-38 (1997)), among others."

In further support that COX-2 inhibitors are useful for the treatment of numerous diseases as combination therapies, Applicants refer to U.S Patent No. 5,858,257, a copy of which is submitted in the Information Disclosure Statement filed on May 18, 2005. At column 3, lines 51 to 55, U.S Patent No. 5,858,257 states:

"The present compounds may also be **used in co-therapies**, partially or completely, in place of other conventional antiinflammatories, such as together with steroids, NSAIDs, 5-lipoxygenase inhibitors, LTB.sub.4 receptor antagonists and LTA.sub.4 hydrolase inhibitors."

At column 4, lines 24 to 44, U.S Patent No. 5,858,257 states:

"The present compounds may also be **used in combination therapies** with opioids and other analgesics, including narcotic analgesics, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic (i.e. non-addictive) analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists and sodium channel blockers, among others. More preferred would be combinations with compounds selected from morphine, meperidine, codeine, pentazocine, buprenorphine, butorphanol, dezocine, meptazinol, hydrocodone, oxycodone, methadone, Tramadol [(+) enantiomer], DuP 747, Dynorphine A, Enadoline, RP-60180, HN-11608, E-2078, ICI-204448, acetominophen (paracetamol), propoxyphene, nalbuphine, E-4018, filenadol, mirtentanil, amitriptyline, DuP631, Tramadol [(-) enantiomer], GP-531, acadesine, AKI-1, AKI-2, GP-1683, GP-3269, 4030W92, tramadol racemate, Dynorphine A, E-

2078, AXC3742, SNX-111, ADL2-1294, ICI-204448, CT-3, CP-99,994, and CP-99,994".

Applicants respectfully traverse the rejection and respectfully submit that the PTO has not established a *prima facie* case of lack of enablement to support a rejection under § 112, first paragraph.

MPEP 2164.01(b) states:

> As long as the specification discloses **at least one method for making and using** the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C § 112 is satisfied. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

MPEP 2164.04 states (emphasis Presented):

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U. S.C. 112, first paragraph, **unless there is reason to doubt the objective truth** of the statements contained therein which must be relied on the enabling support.
>
> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to **explain *why* it doubts the truth or accuracy** of any statement in a supportive disclosure and **to back up assertions of its own with acceptable evidence or reasoning** which is inconsistent with the contested statement.

Applicants respectfully submit that the PTO has not provided ***any evidence or reason*** to doubt the truth or accuracy of the statements in the application that the claimed COX-2 inhibiting compounds are useful for treating the claimed diseases and disorders. The PTO merely provides conclusory statements as to an alleged lack of enablement.

If the PTO maintains this rejection, Applicants respectfully request that the PTO ***provide evidence in the form of scientific literature or publications*** why one skilled in the art would doubt that the claimed compounds would be useful in the claimed methods. The PTO has not provided any evidence to doubt that the presently claimed compounds and compositions can be used to prevent the claimed diseases and/or disorders. MPEP 2164.04.

In view of the above, Applicants respectfully submit that the claims satisfy the requirement under 35 U.S.C. § 112, first paragraph, and respectfully request that the rejection under this provision be withdrawn.

II. Second Rejection under 35 U.S.C. §112, First Paragraph

Claims 59-116 are rejected under 35 USC § 112, first paragraph, as lacking enablement.

Applicants respectfully traverse the rejection and respectfully submit that the claims satisfy the requirements under 35 U.S.C. § 112, first paragraph.

The PTO asserts that the specification is only enabled for the making and using the compound of Example 1. As discussed above, the discussion of which is incorporated herein in its entirety, Applications at page 120, Table 1, have shown that **six** compounds, all encompassed by the compound of Formula (II), are COX-2 selective inhibitors. Additionally there are numerous scientific publications discussing the methods of use of selective COX-2 inhibitor compounds alone or as combination therapies for the treatment of numerous diseases and disorders.

In view of the above, Applicants respectfully submit that the claims satisfy the requirement under 35 U.S.C. § 112, first paragraph, and respectfully request that the rejection under this provision be withdrawn.

III. Rejection under 35 U.S.C. §112, Second Paragraph

Claims 59-116 are rejected under 35 USC § 112, second paragraph, as being indefinite.

Applicants traverse the rejection and respectfully submit that the invention fully complies with the requirement under 35 U.S.C. §112, second paragraph.. As discussed above, the discussion of which is incorporated herein in its entirety, the specification is fully enabled for the methods of use for the compounds of Formula (II) alone and as combination therapies. To that end, Applicants direct the Examiner's attention to the Summary of the Invention at page 2, line 25 to page 6, line 15.

In view thereof, Applicants respectfully submit that the claims satisfy the requirement under 35 U.S.C. § 112, second paragraph, and respectfully request that the rejection under this provision be withdrawn.

IV. Conclusion

Applicants respectfully request reconsideration and allowance of claims 59-116.

Examiner Solola is encouraged to contact the undersigned concerning any questions about the present application.

Respectfully submitted,

Belinda M. Lew, Ph.D.
Registration No. 53,212

Date: July 17, 2006
WILMER HALE LLP
1875 Pennsylvania Avenue, NW
Washington, DC 20006
Phone: (202) 663-6029